REMARKS

This Reply is submitted in response to the Office Action mailed on May 18, 2005. Applicants request respectfully that the Examiner enter the proposed amendments, reconsider the patentability of the claimed invention, and withdraw the rejections issued in the current Office Action.

Status of the Claims

On April 18, 2005, applicants made a species election in response to the Office Action dated March 18, 2005. In so doing, claims 8, 9, 59, 60 and 67-86 were withdrawn from further consideration without prejudice. Claims 18-20 and 52 are canceled herein (claims 8, 40, 43-46 and 48 were canceled previously). Claims 1, 12, 39, 41, 47, 53, and 63-65 are amended herein as set forth in the above Listing of Claims. New claims 87-109 have been added. Accordingly, claims 1, 3-7, 10-17, 21-39, 41, 42, 47, 49-51, 53-58, 61-66 and 87-109 are now presented for the Examiner's consideration.

Support for new claim 87 is found at page 4, line 27 to page 5, line 16, and at page 8, line 25 to page 9, line 4, which describe a solid oral dosage form containing a drug and, as the only enhancer present in the dosage form, a medium chain fatty acid salt which is solid at room temperature. Additional support is found in Example 2, page 20, line 25 to page 21, line 5 which describes the preparation of tablet dosage forms containing a drug and a fatty acid sodium salt as the only enhancer present in the tablet.

New claims 88-105 are directed to compositions and methods for making such compositions. Claims 88 and 98 are supported generally by the methods of claims 41 and 64, and by the examples, and claims 88-105 are further supported by and correspond to existing claims as follows:

New Claim	Existing Claim
88	1
89	3
90	4
91	5
92	6
93	7
94	10
96	41
97	42

98	53
99	54
100	55
101	56
102	57
103	58
104	61
105	64

Claims 106-109 are composition and dosage form claims specific to the use of low molecular weight heparin as the drug and sodium caprate as the enhancer, and support for such claims is found in Example 5, page 27, line 21 to page 29, line 3, and Example 6, page 29, line 9 to page 30, line 24, each of which describe the preparation of a tablet dosage form containing heparin and, as the only enhancer present in the dosage form, sodium caprate.

Summary of the Office Action Mailed May 18, 2005

The Office Action sets forth three separate claim rejections under 35 U.S.C. § 102 and four separate claim rejections under 35 U.S.C. § 103. As support for these rejections, the Examiner cites three primary publications, each of which separately forms the basis for the three § 102 rejections, and in combination, form the basis for the first § 103 rejection. These primary references in various combinations with two additional publications form the bases for the three other § 103 rejections. These rejections and the sets of claims rejected thereunder are summarized as follows.

Rejections under 35 U.S.C. § 102

Claims 1, 3-7, 10-39, 47, 49-58, and 61-66 stand rejected under 35 U.S.C. § 102 based on Published International Application No. WO 97/05903 to Watts et. al ("Watts").

Claims 1, 3-6, 10-13, 26-28, 39, 52-57 and 61-66 stand rejected under 35 U.S.C. § 102 based on Inamori et al., Proc. Int'l Symp. Control. Rel. Bioact. Mat. 24th (1997), pp. 283-284 ("Inamori").

Claims 1, 3, 6, 10-14, 16-28, 33-39, 41, 42, 47, 52-54, 57 and 61-66 stand rejected under 35 U.S.C. § 102 based on Published International Application No. WO 84/04674 to Jang ("Jang").

Rejections under 35 U.S.C. § 103

Claims 1, 3-7, 10-39, 41, 42, 47, 49-58 and 61-66 stand rejected under 35 U.S.C. § 103 as unpatentable over Watts in view of Jang and/or Inamori.

Claims 1, 3-7, 10-39, 41, 42, 47, 49-58 and 61-66 stand rejected under 35 U.S.C. § 103 as unpatentable over Watts in view of Jang and/or Inamori and further in view of Published International Application No. WO 95/22319 to Briskin et al. ("Briskin").

Claims 1, 3-7, 10-13, 26-28, 39, 52-58 and 61-66 stand rejected under 35 U.S.C. § 103 as unpatentable over Inamori in view of U.S. Patent No. 5,714,477 to Einarsson ("Einarsson") and/or Watts.

Claims 1, 3, 6, 7, 10-14, 16-28, 33-39, 41, 42, 47, 52-54, 57, 58 and 61-66 stand rejected under 35 U.S.C. § 103 as unpatentable over Jang in view of Einarsson and/or Watts.

Each of these rejections is traversed respectfully and will be discussed more fully below after the presentation of a summary of the applicants' invention and of the disclosures of each of the cited references.

Summary of Applicants' Invention

Applicants have surprisingly found that, for a given concentration of an orally administered drug, the amount of a drug absorbed across membranes of the gastrointestinal tract can be increased (that is, enhanced) to yield a therapeutically significant increase in serum level of the drug by administering orally a solid dosage form which contains the drug, and, as an enhancer, one or more of the fatty acid salts and/or derivatives as defined in the claims of the present application.

Applicants' amended claims are directed to a solid oral dosage form comprising a hydrophilic or macromolecular drug and, as an enhancer for delivery to the intestine, a salt of a medium chain fatty acid or derivative thereof having a carbon chain length of from 6 to 20 carbon atoms. In addition, there have been added to the application claims which define a composition that is capable of being formulated into a solid oral dosage form and which is referred to herein for convenience as a "precursor composition."

Applicants' claims define two basic embodiments. In one claimed embodiment, referred to herein as the "all-solids" embodiment, the dosage form, the precursor

composition, and each of the constituents thereof are solids at room temperature. Independent claims 1, 39, 41, 47, 88, 96 and 106, and the claims depending therefrom, are directed to the all-solids embodiment. In the other claimed embodiment, referred to herein as the "single enhancer" embodiment, the dosage form and the precursor composition are defined such that the only enhancer present therein is one or more of applicants' fatty acid salt enhancers. Independent claims 53, 63, 64, 65, 98, 105 and 108, and the claims depending therefrom, are directed to the single enhancer embodiment.

In addition, Claims 66, 87, and 95 define an embodiment which includes both the "all-solids" and "single enhancer" recitations.

For either of the two embodiments, the solid oral dosage form can be a tablet, a capsule, or a multiparticulate, and the multiparticulate may itself be in the form of a tablet or contained within a capsule. The dosage form may also be provided in a controlled release dosage form such as, for example, a delayed release dosage form. In one embodiment, the dosage form is a delayed release rapid onset dosage form. In such controlled release dosage forms, a rate-controlling or delayed release polymer coating may be included to provide the desired release characteristics.

The drug component of the presently claimed invention is any hydrophilic or macromolecular drug appropriate for administration via the oral route. The terms "hydrophilic" and "macromolecular" are found in the specification at page 9, line 26. Examples of the drug component include peptides, proteins, oligosaccharides, polysaccharides, and hormones as recited at page 9, lines 24-27 of the specification.

As is generally understood in the art, hydrophilic is a term meaning "water-loving" and refers to a molecular entity "having an affinity for, absorbing, wetting smoothly with, tending to combine with, or capable of dissolving in water." See *The American Heritage Dictionary* (Second College Edition 1991) at 631, attached as part of Appendix 1 to this Reply. Macromolecular is understood to refer to molecular entities having a molecular weight of at least 1,000. See *Hackh's Chemical Dictionary* (4th Ed., 1969) at 400, attached as part of Appendix 1 to this Reply.

The enhancer component of the present invention is defined as being a salt of a fatty acid, or a halide, anhydride, or glyceride derivative of a fatty acid, having a carbon chain length of from 6 to 20 carbon atoms that is capable of enhancing the transport of a

drug, particularly a hydrophilic and/or macromolecular drug, across the gastrointestinal tract (GIT) in an animal such as a human. Preferably, the enhancer is a sodium salt of a medium chain fatty acid, and most preferably, sodium caprate.

The all-solids dosage forms are prepared conveniently from admixtures of constituents which are a solid at room temperature. By not using liquid or semi-solid constituents in the admixture, the compositions are provided in a form that offers many benefits in manufacture including an avoidance of the need to place such liquid constituents into a solid form during preparation, for example, by encapsulation of the liquids, the simplification of equipment requirements and personnel training, the reduction in the number of unit operations for the preparation of the dosage forms, the ability to produce different controlled release formulations, and ease of administration.

The discussion which follows shows clearly that the publications cited in the Office Action neither teach nor suggest applicants' claimed precursor compositions or dosage forms, the related methods for preparing the aforementioned or the use thereof.

Summary of the Cited Publications

1. **International Application No. WO97/05903 (Watts)**

Watts discloses liquid or semi-solid compositions for colonic delivery comprising a drug and an absorption promoter for enhancing transport of a polar drug across the membrane of the colon. At page 5, lines 10-16, the composition of Watts is defined as comprising:

> a polar drug,
> an absorption promoter which
> (a) comprises a mixture of a fatty acid having 6 to 16 carbon atoms or a salt thereof and a dispersing agent
> or
> (b) comprises a mixture of mono/diglycerides of medium chain fatty acids and a dispersing agent and
> means adapted to release the polar drug and absorption promoter in the colon.

Significantly, the compositions of Watts are defined as either a liquid or a semi-solid (page 8, line 21). Watts further teaches the functional advantages provided by the liquid or semi-solid states of the compositions as they "form a readily dispersing mixture when the capsule in which they are filled disintegrates" and will "spontaneously emulsify in contact with aqueous media (e.g. intestinal fluid)." (page 9, lines 5 to 12).

With regard specifically to the dispersing agent component of the multi-component absorption promoter of Watts, this is an essential component that Watts describes as comprising one or more constituents which promote the dispersion of the composition within the lumen of the colon (page 6, line 4). Thus, according to Watts, the dispersing agent is acting to enhance drug absorption and its presence in the multi-component absorption promoter of Watts, along with the fatty acid material, means that the compositions of Watts are disclosed as comprising at least *two* types of absorption enhancers. Additionally, and consistent with the other teachings of Watts, all of the dispersing agents that are used in the Watts working examples are liquids.

Consistent with the Watts mandate that composition be in either a liquid or semi-solid form, Watts discloses a series of ten examples which are illustrative of embodiments of his composition and each of which describes the preparation of a composition comprising a drug and a mixture of either a fatty acid or a mono/diglyceride of a medium chain fatty acid with a liquid dispersing agent. Each of the dispersing agents used in illustrative Examples 1 and 4-12 is a liquid at room temperature. In these examples, the preparation of the dosage form begins with a liquid mixture of a medium chain fatty acid or a mono/diglyceride of a medium chain fatty acid and a liquid dispersing agent.

Comparative Example 2 contains a liquid dispersing agent. Comparative Example 3 does not include a dispersing agent and it includes a fatty acid not a salt of a fatty acid.

Significantly, and as discussed in greater detail below, Watts teaches that when fatty acids are used as an absorption enhancer in the absence of a dispersing agent they are not effective in enhancing drug absorption (page 13, lines 24 to 28). As shown in comparative Example 3, a composition is prepared comprising a drug and a fatty acid as the only absorption enhancer. Notably, this composition fails to provide enhanced

absorption of the drug, and the lack of absorption enhancement is attributed to the lack of a dispersing agent which, as explained in Watts, is taught to have a synergistic effect with the fatty acid.

In summary, Watts neither teaches nor suggests the preparation of a composition comprising constituents, all of which are solid at room temperature and includes a fatty acid salt, nor the preparation of a dosage form which contains, as the only enhancer present in the dosage form, one or more members of the group consisting of a fatty acid salt, halide, anhydride glyceride, and difunctional fatty acid derivatives.

2. ***Absorption Enhancement of Argatroban by Medium Chain Fatty Acid Sodium Salts*, Inamori, et al. Proceed. Int'l. Symp. Control, Bioact. Mater., 24 (1997) 283-284**

The purpose of the study reported in Inamori was to examine the bioavailiability characteristics of argatroban, a low-solubility (i.e., hydrophobic), low molecular weight (m.w. 526.66) anti-thrombin drug, and the use of medium chain fatty acid sodium salts as absorption enhancers. As an initial matter, it is important to note that the disclosure of Inamori is limited and as a result it is unclear what was done. Specifically, while several dosage forms of argatroban are discussed, there is no disclosure at all of details of the dosage form, other excipients used, whether other components are present that may act as enhancers, how many were made, and how they were administered to test animals.

According to Inamori, medium chain fatty acid sodium salts having 6, 8, 10, 12 and 16 carbon atoms were considered as potential absorption enhancers, and C10 was found to have the highest AUC and C_{max} and, therefore, to be the most effective. C10 was also found to exhibit greater values for AUC and C_{max} as the relative proportion of C10 was increased.

Various dosage forms for oral administration were evaluated. Inamori describes the following forms:

Conventional formulation tablet

Argatroban solution in pH 2 solvent

Physical mixture of argatroban and C10

Fast-release granules (solution of argatroban and C10 sprayed on cores)

Enteric-coated granules

As noted above, Inamori does not describe in any detail the manner in which the first three of these dosage forms were prepared, nor does it disclose the manner in which any of these dosage forms was administered to test animals.

In comparing the plasma level profiles associated with the administration of these dosage forms, Inamori observed that the highest plasma level (measured in μg/ml) was exhibited by the physical mixture (Fig. 3). The next highest was the pH 2 solution, followed by the conventional tablet (Fig. 3). The plasma level of the fast-release granules was almost the same as the physical mixture, and the plasma level associated with enteric-coated granules was lower compared with the fast-release granules (Fig. 4). From these, Inamori concludes with the observation that C10 was available for argatroban as an absorption enhancer, and that drug absorption was enhanced by three to five times compared with that of the conventional tablet.

In theorizing as to the responsible mechanism, Inamori suggests that the C10 assists in dissolving the argatroban and functions as a surfactant. It is important to note that argatroban has a low solubility and is considered hydrophobic. As a result, the effect of such a mechanism in the dosage forms of Inamori would be to place greater amounts of argatroban in solution to be more readily and immediately absorbed in the stomach.

Notably, the data of Inamori show greater bioavailability associated with immediate release dosage forms as compared with enteric-coated forms (Figs. 4 and 5). Specifically, Fig. 5 shows plots of plasma levels over time for three different combinations of fast release granules and enteric-coated granules. As is evident from the plots, the AUC is greatest for the combination of granules with a ratio weighted 2:1 fast to enteric, less for equal amounts of fast and enteric granules, and the least for the combination of granules with the ratio weighted 1:2 fast to enteric. From these data, the mechanism by which C10 acts in the formula identified by Inamori (whatever that formula may be) as an absorption enhancer for low solubility drugs is confirmed to involve assisting in the dissolution of the drugs making them more available for immediate release. As a result, the teachings of Inamori are limited to the use of low solubility drugs and C10 as a surfactant.

3. **International Application No. WO 84/04674 to Jang**

Jang describes compositions in the form of controlled-release dosage forms for oral administration. According to Jang, the compositions are formulated in a manner such that problems associated with solvent residue, heat damage and tablet integrity are overcome. For this purpose, Jang describes a compressed composition of superior physical integrity and resistance to delamination.

The compositions of Jang comprise a combination of an (1) active; (2) matrix of either a hydrophobic carbohydrate polymer or an admixture containing a hydrophobic carbohydrate polymer and from one to three digestive-difficulty soluble components. The three digestive-difficulty soluble components which can be used are (1) a wax; (2) a fatty acid material such as a fatty acid having from 12-28 carbon atoms, a fatty alcohol having from 16 to 44 carbon atoms, a fatty amine having from 13 to 45 carbon atoms, or a fatty amide having from 11 to 45 carbon atoms; or (3) a neutral lipid.

The active is broadly defined as "all substances which when introduced into the body of a human, animal, plants, soil and water is biologically active, usually in a therapeutic sense, nutritional purpose or biocidal effects." (page 6, lines 22-25). Representative actives are then listed by drug class and include anticoagulant drugs such as warfarin. Heparin is not specifically mentioned.

The disclosure of the fatty acid materials is limited to fatty acids, fatty alcohols, fatty amines and fatty amides. The preferred fatty acid materials are disclosed as fatty acids having 12 to 28 carbons, fatty alcohols having from 16 to 44 carbons, and fatty amines having from 11 to 45 carbons. The most preferred fatty acid material (and the one used in all of the disclosed examples) is hystrene which is a mixture of 85% stearic acid (C18) and 15% palmitic acid (C16). There is no disclosure at all in Jang of the use of fatty acid salts, or halide, anhydride or glyceride derivatives of fatty acids.

4. **International Application No. WO 95/22319 to Briskin et al. ("Briskin")**

Briskin is directed to a method for making fine particulate formulations that can be used to administer therapeutically active compounds. Briskin is cited in the Office Action solely for its disclosure on page 3 of broad range of pharmaceutically acceptable

salts of the therapeutically active compounds disclosed in Briskin including halogen salts such as hydrobromide and hydrochloride.

5. **US Patent No. 5,714,477 to Einarsson ("Einarsson")**

Einarsson is directed to pharmaceutical compositions containing heparin or heparin fragments or their derivatives in combination with one or more glycerol esters of at least one fatty acid. Notably, all of the compositions exemplified in Einarsson are in liquid form, and there is no disclosure of the use of salts of medium chain fatty acids.

Discussion of Claim Rejections

Anticipation Under 35 U.S.C. § 102

A rejection under 35 U.S.C. § 102 is proper only if each and every element of the claim is found in a single prior art reference, arranged as in the claim. MPEP § 2131; *Brown v. 3M*, 265 F.3d 1349, 60 USPQ2d 1375 (Fed. Cir. 2001). The corollary entailed by this principle is that where a cited reference does not contain each and every element of the claim, it cannot support a rejection under 35 U.S.C. § 102.

The Claim Rejection Under § 102 Based on Watts

Claims 1, 3-7, 10-39, 47, 49-58, and 61-66 stand rejected under 35 U.S.C. § 102 as being anticipated by Watts, or in the alternative, as prima facie obvious over Watts. These rejections are traversed respectfully.

Rejected independent Claims 1, 39, and 47, which define the all solids embodiment of applicants' invention, distinguish over the Watts disclosure in reciting the dosage for is a solid and further that... "each of said constituents and any other constituent comprising the composition is a solid at room temperature." The Examiner has, in effect, acknowledged that the aforementioned "solids" definition does in fact distinguish over the Watts disclosure, but has taken the position that the words comprising the definition are considered to be meaningless. In the Examiner's view, the words are not afforded patentable weight because they refer to the physical state of the constituents comprising the composition. Such constituents are characterized by the

Examiner as being "intermediates."

The Examiner's anticipatory rejection and his explanation of the basis for the rejection are founded on his view that applicants' composition claims are not in fact composition claims, they are product-by-process claims (see Office Action, page 3, paragraph 3, lines 13 to 15). The Examiner has not in any way explained the legal basis that permits him to treat a composition claim (which has absolutely no process terms associated with it) as being a product-by-process claim in order to justify a § 102 rejection.

Let there be no question. There are absolutely no terms in applicants' composition claims that can in any way be construed as involving process steps. This is plain on its face. Furthermore, as mentioned above, the Examiner has not cited any authority which gives an Examiner the legal basis to treat a composition claim as a product-by-process claim in an effort to justify an anticipatory rejection in a situation where the "non-product-by-process" claims clearly distinguish over the prior art. If the Examiner is aware of such authority, it is requested respectfully that the authority be cited.

The Examiner is reminded respectfully that product-by-process claims were developed initially as a means to define a composition (or other product) that was not capable of being defined by the constituents comprising the product; they are a valuable and practical claim form. However, they are not available for use by an Examiner to impose "scope" restrictions which are associated with such claims on a perfectly proper composition claim in which the constituents comprising the composition are capable of being defined and, indeed, are defined and in addition, in a way that distinguishes over the prior art. The Examiner's attention is directed respectfully to the MPEP, Section 2113(Eight Edition, August 2001, Latest Revision May 2004) which discusses product-by-process claims. The discussion makes abundantly clear that a necessary element of a product-by-process claim is that the claim contain one or more process steps.

The Examiner's characterizations of the constituents of applicants' claimed composition as being intermediates in order to justify his anticipatory rejection also finds no basis in fact or law. Applicants' claimed constituents are what they are, that is, they are elements comprising the composition and their physical properties are such that they

are solids at room temperature. If one were to extend the Examiner's rationale to composition claims in general, any constituent which comprises a composition and which is characterized in the claim by its physical properties would be an intermediate that is not afforded patentable weight. Applicants are not aware of a legal basis which supports the Examiner's position. If the Examiner is aware of law which supports his position, it is requested respectfully that he identify it.

In summary, applicants submit that it is apparent that the Examiner has recognized that applicants' all-solids claims do in fact distinguish over the Watts disclosure, but, in an effort to justify issuance of an anticipatory rejection, the Examiner has seized upon an illogical rationale for rejection which involves ignoring the "distinguishing" claim terms. This is not in accordance with the law which requires that all terms of a claim must be considered and given weight when evaluating the patentability of the claim over the prior art (see *Ex Parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), aff'd mem., 738 F. 2d 453 (Fed. Cir. 1984)). Accordingly, it is requested respectfully that the anticipatory rejection based on Watts regarding applicants' all-solids claims be withdrawn.

With regard to applicants' single enhancer claims (independent Claims 53, 63-65, and now also 98, 105 and 108), these claims distinguish over Watts as they define a composition which includes a fatty acid salt (or derivative as set forth in the claims) as the only enhancer in the composition. In contrast, the Watts composition includes both a fatty acid or salt and another enhancer in the form of a dispersing agent which is an essential component of the Watts composition.

As described by Watts, the enhancing function of the dispersing agent is its ability to promote a dispersion of the Watts composition within the lumen of the colon (Watts at page 6, line 4). As discussed above in the summary of Watts, Watts presents test data showing enhanced drug absorption for the compositions of Watts but not for comparative compositions containing the drug and either a fatty acid or a dispersing agent but not both (see example 1 and comparative examples 2 and 3 and figures 1 to 3 of Watts). Watts attributes the lack of enhanced absorption of the comparative composition containing the fatty acid to the absence of the dispersing agent. Accordingly, applicants' single enhancer claims distinguish over Watts by defining compositions and dosage forms

which include a fatty acid salt (or derivative as set forth in the claims) as the only enhancer in the composition. It is requested respectfully that the anticipation rejection regarding the single enhancer claims based on Watts be withdrawn.

With regard to the Examiner's alternative rejection under § 103 based on Watts, it is clear that there is no disclosure in Watts that would lead one to modify the composition to solid form or omit the dispersing agent taught to be essential in Watts. In view of these teachings, Watts does not make obvious the provision of either an all-solid composition or a composition in which the sole enhancer is a medium chain fatty acid salt or derivative thereof. Accordingly, it is requested respectfully that the rejection under § 103 based on Watts be withdrawn.

The Claim Rejection Under § 102 Based on Inamori

Claims 1, 3-6, 10-13, 26-28, 39, 52-57 and 61-66 stand rejected under 35 U.S.C. § 102 based on Inamori. This rejection is traversed respectfully.

The claims of the present application in their amended form distinguish over Inamori in defining the drug constituent as being a hydrophilic or macromolecular drug. The only drug referred to in the Inamori reference is argatroban which is a compound that is neither hydrophilic nor macromolecular. As discussed above, the term hydrophilic is understood in the art as to mean "having an affinity for, absorbing, wetting smoothly with, tending to combine with, or capable of dissolving in water." See *The American Heritage Dictionary*, Second College Edition (1991) at 631, attached as part of Appendix 1 to this Reply. Similarly, the term macromolecular is understood to refer to molecular entities having a molecular weight of at least 1,000. See *Hackh's Chemical Dictionary*, (4th Ed., 1969) at 400, attached as part of Appendix 1 to this Reply. In contrast, and as discussed above, argatroban has low solubility in water (i.e., hydrophobic) and a molecular weight of 526. Because the disclosure of Inamori are limited to the use of C10 as a surfactant for a low molecular weight, hydrophobic drug to assist in dissolving the drug for immediate uptake, Inamori does not teach or suggest the presently claimed invention. There is nothing in Inamori that teaches or suggests the use of C10 or indeed any other fatty acid for delivery to the intestine of a patient as an absorption enhancer for hydrophilic or macromolecular drugs. In the absence of any disclosure in Inamori that

C10 acts as an absorption enhancer in the intestine with hydrophilic or macromolecular drugs, Inamori fails to teach each and every element of claims 1, 3-6, 10-13, 26-28, 39, 52-57 and 61-66. As a consequence, the anticipatory rejection based on Inamori is without adequate support and it is requested respectfully that the rejection be withdrawn.

The Claim Rejection Under § 102 Based on Jang

Claims 1, 3, 6, 10-14, 16-28, 33-39, 41, 42, 47, 52-54, 57 and 61-66 stand rejected under 35 U.S.C. § 102 based on Jang. This rejection is traversed respectfully.

The claims of the present application in their amended form distinguish over Jang in defining the enhancer constituent as being a salt of a fatty acid, or a halide, anhydride or glyceride derivative of a fatty acid. As set forth above in the summary of the Jang reference, this publication does not disclose salts. Jang discloses fatty acid materials which are identified as fatty acids, fatty alcohols, fatty amines and fatty amides. Because Jang does not disclose the use of a salt of a fatty acid, or a halide, anhydride or glyceride derivative of a fatty acid, it fails to teach each and every element of claims 1, 3, 6, 10-14, 16-28, 33-39, 41, 42, 47, 52-54, 57 and 61-66. Accordingly, it is respectfully requested that the § 102 rejection based on Jang be withdrawn.

Obviousness Under 35 U.S.C. § 103

In order to establish a *prima facie* case of obviousness, the involved references must teach or suggest all of the claim limitations and it must be shown that there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the disclosures of the references, and that there is a reasonable expectation of success. When applying § 103, the following tenets of patent law must be adhered to:

(A) the claimed invention must be considered as a whole;

(B) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) reasonable expectation of success is the standard with which obviousness is determined.

See MPEP § 2141; *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

The Claim Rejection Under § 103 Based on Watts in view of Jang and/or Inamori

Claims 1, 3-7, 10-39, 41, 42, 47, 49-58 and 61-66 stand rejected under 35 U.S.C. § 103 as unpatentable over Watts in view of Jang and/or Inamori. This rejection is traversed respectfully.

In the Office Action, the Examiner concedes that Watts fails to teach dry direct compression of its composition components to form tablets or granulates for capsule incorporation. This concession is consistent with the teachings of Watts as a whole. Watts is directed to liquid or semi-solid compositions, and Watts emphasizes the importance of the liquid or semi-solid form of its compositions by the recitation of advantages associated with such form.

In recognition of the shortcomings of Watts, the Examiner has combined the teachings of Watts with those of Inamori and/or Jang. Yet in combining these teachings, the Examiner has not satisfied the applicable principles of patent law regarding obviousness as set forth above. Considering the references as a whole, there is no suggestion whatsoever of the desirability of combining the teachings of either Inamori or Jang which are directed to solid compositions with the liquid or semi-solid compositions of Watts. The solid formulations of Inamori and the dry, direct compression processes of Jang are simply incompatible with the liquid or semi-solid compositions of Watts. This basic incompatibility not only fails to provide motivation to combine these references, but also negates any reasonable expectation of success in doing so. As a result, neither Jang nor Inamori, either separately or in combination, may be combined with the

teachings of Watts to formulate the compositions of Watts by a dry, direct compression process.

Watts is also directed to compositions of a drug and an absorption enhancer that comprises either (a) a mixture of a fatty acid having 6 to 16 carbon atoms or a salt thereof and a dispersing agent; or (b) a mixture of mono/diglycerides of medium chain fatty acids and a dispersing agent. As a result, assuming the basic incompatibility of these references is ignored, the combination of Watts with either Inamori or Jang would not result in a composition in which the fatty acid component is the sole enhancer present in the formulation. There is no suggestion in Jang or Inamori of the desirability of modifying the compositions of Watts to remove the dispersing agent, which Watts considers critical, nor is there anything in any of the references that would provide a reasonable expectation of success in doing so. Simply put, by combining Watts with either or both Inamori and Jang, one does not arrive at the presently claimed invention, either in its all-solids embodiment or in its single enhancer embodiment. Accordingly, the obviousness rejection based on Watts in view of Jang and/or Inamori should be withdrawn.

The Claim Rejection Under § 103 Based on
Watts in view of Jang and/or Inamori and Briskin

Claims 1, 3-7, 10-39, 41, 42, 47, 49-58 and 61-66 stand rejected under 35 U.S.C. § 103 as unpatentable over Watts in view of Jang and/or Inamori and further in view of Briskin. This rejection is traversed respectfully.

As set forth above, the combination of Watts with either or both of Jang and Inamori is insufficient to support an obviousness rejection of the presently claimed invention. None of these references, either singly or in combination, teaches or suggests all of the recitations of either the all-solids embodiment or the single enhancer embodiment.

In this rejection, the Examiner has combined the teachings of Watts and Inamori and/or Jang with Briskin for the limited purpose of supporting the substitution of sodium salts with halogen salts. Yet in combining these teachings, the Examiner has not satisfied the applicable principles of patent law regarding obviousness as set forth above.

Considering the references as a whole, there is no suggestion whatsoever of the desirability of combining the teachings of the liquid or semi-solid compositions of Watts with the solid compositions of either Inamori or Jang and the halogen salts of Briskin. To the extent the primary references (namely, Watts, Inamori and Jang) neither teach nor suggest the claimed invention, the addition of Briskin for the limited purpose of suggesting the substitutability of halogen salts for sodium salts does not cure the basic infirmities of the primary reference. Accordingly, the obviousness rejection based on Watts in view of Jang and/or Inamori and further in view of Briskin should be withdrawn.

The Claim Rejection Under § 103 Based on
Inamori in view of Einarsson and/or Watts

Claims 1, 3-7, 10-13, 26-28, 39, 52-58 and 61-66 stand rejected under 35 U.S.C. § 103 as unpatentable over Inamori in view of U.S. Patent No. 5,714,477 to Einarsson ("Einarsson") and/or Watts. This rejection is traversed respectfully.

In this rejection, the Examiner has combined the teachings of Watts and Inamori and/or Jang with Einarsson for the limited purpose of suggesting the use of heparin and its low molecular fragments in combination with one or more glycerol esters of at least one fatty acid. Yet in combining these teachings, the Examiner has not satisfied the applicable principles of patent law regarding obviousness as set forth above. As noted above, there is nothing in Inamori that teaches or suggests the use of either a hydrophilic or macromolecular drug with a fatty acid as an absorption enhancer for delivery to the intestine of a patient. Importantly, all of the compositions exemplified in Einarsson, as in Watts, are in liquid form. As a result, the combination of Inamori with either or both Einarsson and Watts would neither teach nor suggest the claimed invention, either the all-solids embodiment or the single enhancer embodiment. Simply put, the combination of Einarsson and/or Watts with Inamori does not cure the basic infirmities of Inamori as set forth above. Accordingly, the obviousness rejection based on Inamori in view of Einarsson and/or Watts should be withdrawn.

The Claim Rejection Under § 103 Based on Jang in view of Einarsson and/or Watts

Claims 1, 3, 6, 7, 10-14, 16-28, 33-39, 41, 42, 47, 52-54, 57, 58 and 61-66 stand rejected under 35 U.S.C. § 103 as unpatentable over Jang in view of Einarsson and/or Watts. This rejection is traversed respectfully.

In this rejection, the Examiner has combined the teachings of Jang with either Einarsson or Watts for the limited purpose of suggesting the use of heparin and its low molecular fragments. Yet in combining these teachings, the Examiner has not satisfied the applicable principles of patent law regarding obviousness as set forth above. As set forth above, Jang discloses a composition comprising a combination of an (1) active; and (2) a matrix of either a hydrophobic carbohydrate polymer or an admixture containing a hydrophobic carbohydrate polymer and from one to three digestive-difficulty soluble components. The three digestive-difficulty soluble components which can be used are (1) a wax; (2) a fatty acid material such as a fatty acid having from 12-28 carbon atoms, a fatty alcohol having from 16 to 44 carbon atoms, a fatty amine having from 13 to 45 carbon atoms, or a fatty amide having from 11 to 45 carbon atoms; or (3) a neutral lipid. There is no disclosure at all in Jang of the use of fatty acid salts or halide, anhydride or glyceride derivatives of fatty acids as intestinal absorption enhancers.

Einarsson and Watts are used for the limited purpose of suggesting the use of heparin and its low molecular fragments. Moreover, all of the compositions exemplified in Einarsson, as in Watts, are in liquid form. As a result, there is no motivation to combine these references and there can be no reasonable expectation of success in doing so. The combination of Jang with Einarsson and/or Watts neither teaches nor suggests the claimed invention, either the all-solids embodiment or the single enhancer embodiment as the addition of Einarsson and/or Watts with Jang does not cure the basic infirmities of Jang as set forth above. Accordingly, the obviousness rejection based on Jang in view of Einarsson and/or Watts should be withdrawn.

Discussion of Added Claims

Applicants have added to the application Claims 88 to 10 which define the "precursor" compositions (and methods for preparing the compositions) that are capable

of being formulated into solid oral dosage forms, for example, as defined in Claims 1 and 53. The added claims include recitations that are present in the "dosage form" claims that define applicants' "all solids" embodiment and/or the "single enhancer" embodiment. As such, the added precursor composition claims distinguish clearly from the compositions disclosed in the references, for example, from the mixture of ingredients from which the Watts end-product is made.

In view of the foregoing amendments and remarks, applicants submit respectfully that the application is in condition for allowance and request respectfully issuance of a Notice of Allowance. If any issues remain, the undersigned requests a telephone interview prior to the issuance of an Action.

Respectfully submitted,

Date: August 5, 2005

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HACKH'S CHEMICAL DICTIONARY

M

M. (1) Symbol for metal. (2) Abbreviation for mega, or million. **M acid.** 1-Amino-5-naphthol-4-sulfonic acid.

M. Symbol for: (1) mass, (2) molal, (3) molecular weight, (4) the mathematical constant $\log_e 10 = 0.43429,44819$. M^{-1} The mathematical constant $\log_e 10 = 2.30258,50930$. ***M* electron.** The electron of the *M* shell or *M* orbit, q.v. ***M* orbit.** The third layer or energy level, in which electrons move around the proton in the dynamic atom. ***M.* radiation.** A series of homogeneous X rays characteristic of the metal used as anticathode, and fainter than the *K* and *L* series. ***M* series.** The spectral lines produced by the *M* radiations on diffraction through a crystal grating. Cf. *Moseley spectra*. ***M* shell.** The third layer or energy level, in which electrons oscillate in the static atom.

m. Abbreviation for: (1) meter, (2) milli-, or one-thousandth part. **m²**. Abbreviation for square meter. **m³**. Abbreviation for cubic meter. Cf. *mm, mmm*.

m. Symbol for: (1) meta position, (2) metastable state.

℥. Abbreviation for minim.

μ. Greek mu. (1) Abbreviation for: (*a*) icron, (*b*)m micro-, or one-millionth of a unit. (2) Symbol for: (*a*) meso position, (*b*) magnetic permeability. Cf. m*μ*, *μμ*.

Ma. Symbol for masurium.

ma. Abbreviation for milliampere.

Mac. See also *Mc*.

macassar oil. Yellow fat from the seeds of *Schleichera trijuga*, India and Malaysia.

mace. Macis. The dried covering tissues of the seeds of *Myristica fragrans;* a condiment. **m. oil.** An essential oil from mace. Colorless liquid, d.0.91; a flavoring.

macene. $C_{10}H_{18} = 138.1$. A terpene from mace oil.

maceral. General name for the microscopic structures of the mineral constituents of coals.

macerate. To break up a solid by soaking in a liquid.

Mache, Heinrich. Austrian physicist. born, 1876.

m. unit. M.E. The quantity of radioactive emanation which produces a saturation current of one-thousandth of an electrostatic unit. 1 curie $= 2.8 \times 10^9$ maches. 1 mache $= 3.64 \times 10^{-10}$ curie/liter $= 3.64$ eman.

machine steel. A steel containing less than 0.3% carbon; easily machined.

macht metal. A forging alloy containing Cu 60, Zn 38, Fe 2%.

Mach unit. A unit of velocity, expressed as a percentage of the velocity of sound at sea level.

mackay bean. The dried seeds of *Entada scandens* (Leguminosae), Queensland; a coffee substitute.

mackenite metals. A group of heat-resisting Ni–Cr or Ni–Cr–Fe alloys.

Mackenzie amalgam. An amalgam made by grinding together the solid alloys Hg–Bi and Pb–Hg.

Mackey test. A test of the autoxidation fire hazards of oils.

maclayine. $C_{17}H_{32}O_{11} = 412.26$. An alkaloid from *Illipe maclayana* (Sapotaceae), the tropics.

macle. (1) A variety of andalusite. (2) A twin crystal.

MacLeod, John James Rickard. 1876–1935. Scottish-Canadian biochemist, awarded Nobel Prize (with Banting) in 1923 for share in discovery of insulin.

macleyine. Protopine.

maclurin. $C_6H_3(OH)_2CO.C_6H_2(OH)_3 = 280.1$. Pentahydroxybenzophenone, osage orange (q.v.), moringatannic acid. Yellow crystals from the wood of *Maclura aurantiaca*, m.200, soluble in hot water; a dye.

macro- Prefix (Greek μακρός = broad), indicating "large."

macroaxis. The long axis in orthorhombic or triclinic crystals.

macrobacterium. A large bacterium.

macrocarpine. An alkaloid from *Thalictrum macrocarpum* (Ranunculaceae). Yellow crystals, soluble in water.

macrochemistry. (1) The chemistry of reactions that are visible to the unaided eye. Cf. *microchemistry*. (2) Chemical operations on a large scale.

macrocyclic. Containing rings of more than 7 C atoms.

macrodome. See *dome*.

macrofarad. Megafarad.

macrograph. Photomacrograph.

macrolide. A substance having a macrocyclic lactone structure; as, streptomycin.

macromolecular chemistry. The study of the preparation, properties, and uses of substances containing large and complex molecules: i.e., mol. wt. exceeding 1,000. Cf. *polymer*.

macroscopic. Describing objects visible to the naked eye. Cf. *microscopic*.

macrotin. Cumicifugin.

macrotoid. The combined principles from the root of *Cimicifuga racemosa;* an antispasmodic.

macrotys. Cimicifuga.

maculanin. Potassium amylate.

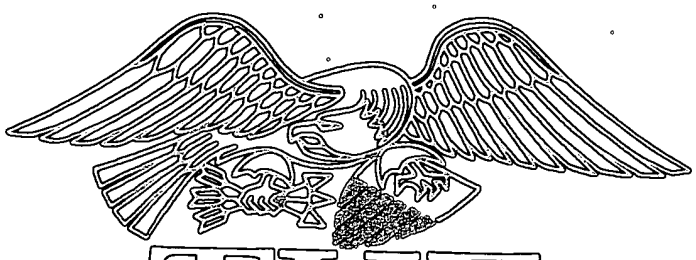
madder. Turkey red, q.v. Garance. The root of *Rubia tinctorum* species. It contains glucosides which yield, on fermentation, alizarin and purpurin; a dye and pigment in lakes.

Maddrell salt. A long-chain, high-molecular-weight sodium metaphosphate, made by heating sodium metaphosphate at 300; soluble in potassium salt solutions.

mafic. A rock-forming material, mainly magnesium and iron silicates.

mafurite. A mineral association of kieserite and augite, q.v.

Quality By Definition



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hy·dro·me·chan·ics (hī′drō-mĭ-kăn′ĭks) *n.* *(used with a sing. verb).* Mechanics dealing with the motion and equilibrium states of fluids. —**hy′dro·me·chan′i·cal** *adj.*

hy·dro·me·du·sa (hī′drō-mĭ-do͞o′sə, -dyo͞o′-) *n.*, *pl.* **-sas** or **-sae** (-sē). A hydrozoan in its medusoid stage. [HYDRO(ID) + MEDUSA.]

hy·dro·mel (hī′drə-mĕl′) *n.* Mead¹. [ME *ydromel* < OFr. < Lat. *hydromel* < Gk. *hudromeli* : *hudōr*, water + *meli*, honey.]

hy·dro·met·al·lur·gy (hī′drō-mĕt′l-ûr′jē) *n.* The separation of metal from ores and ore concentrates by chemical reactions in aqueous solution, as leaching, extraction, and precipitation. —**hy′dro·met′al·lur′gi·cal** *adj.*

hy·dro·me·te·or (hī′drō-mē′tē-ər, -ôr′) *n.* A precipitation body, such as rain, snow, sleet, or hail, derived from the condensation of water in the atmosphere.

hy·dro·me·te·or·ol·o·gy (hī′drō-mē′tē-ə-rŏl′ə-jē) *n.* The meteorology of the occurrence, motion, and changes of state of atmospheric water. —**hy′dro·me′te·or′o·log′i·cal** (-ôr′ə-lŏj′ĭ-kəl, -ŏr′-) *adj.* —**hy′dro·me′te·or·ol′o·gist** *n.*

hy·drom·e·ter (hī-drŏm′ĭ-tər) *n.* An instrument used to determine specific gravity, esp. a sealed, graduated tube, weighted at one end, that sinks in a fluid to a depth used as a measure of the fluid's specific gravity. —**hy′dro·met′ric** (hī′drə-mĕt′rĭk), **hy′dro·met′ri·cal** *adj.* —**hy′dro·met′ri·cal·ly** *adv.* —**hy·drom′e·try** *n.*

hy·dro·ni·um (hī-drō′nē-əm) *n.* A hydrated hydrogen ion, H_3O^+. [HYDR(O)- + (AMM)ONIUM.]

hy·drop·a·thy (hī-drŏp′ə-thē) *n.* The therapeutic use of water. —**hy′dro·path′ic** (hī′drə-păth′ĭk), **hy′dro·path′i·cal** *adj.* —**hy·drop′a·thist, hy′dro·path′** *n.*

hy·dro·phane (hī′drə-fān′) *n.* An opal that is almost opaque when dry but transparent when wet. —**hy·droph′a·nous** (hī-drŏf′ə-nəs) *adj.*

hy·dro·phil·ic (hī′drə-fĭl′ĭk) *adj.* Having an affinity for, absorbing, wetting smoothly with, tending to combine with, or capable of dissolving in water. [NLat. *hydrophilus*, hydrophilous + -IC.] —**hy′dro·phile′** (hī′drə-fīl′) *n.* —**hy′dro·phi·lic′i·ty** (-fə-lĭs′ĭ-tē) *n.*

hy·droph·i·lous (hī-drŏf′ə-ləs) *adj.* *Bot.* Growing or thriving in water. —**hy·droph′i·ly** *n.*

hy·dro·pho·bi·a (hī′drə-fō′bē-ə) *n.* **1.** Fear of water. **2.** Rabies.

hy·dro·pho·bic (hī′drə-fō′bĭk, -fŏb′ĭk) *adj.* **1.** Antagonistic to, shedding, tending not to combine with, or incapable of dissolving in water. **2.** Of or exhibiting hydrophobia. —**hy′dro·pho·bic′i·ty** (-bĭs′ĭ-tē) *n.*

hy·dro·phone (hī′drə-fōn′) *n.* An electrical instrument for detecting or monitoring sound under water.

hy·dro·phyte (hī′drə-fīt′) *n.* A plant that grows in and is adapted to an aquatic or very wet environment. —**hy′dro·phyt′ic** (-fĭt′ĭk) *adj.*

hy·dro·plane (hī′drə-plān′) *n.* **1.** A seaplane. **2.** A motorboat designed so that the prow and much of the hull lift out of the water and skim the surface at high speeds. **3.** A hydrofoil (sense 2). **4.** A horizontal rudder on a submarine. —*intr.v.* **-planed, -plan·ing, -planes. 1.** To drive or ride in a hydroplane. **2. a.** To skim along on the surface of the water. **b.** To be or go out of control by skimming along the surface of a wet road. Used of a car.

hy·dro·pon·ics (hī′drə-pŏn′ĭks) *n.* *(used with a sing. verb).* The cultivation of plants in water containing dissolved inorganic nutrients, rather than in soil. [HYDRO- + (GEO)PONICS.] —**hy′dro·pon′ic** *adj.* —**hy′dro·pon′i·cal·ly** *adv.* —**hy′dro·pon′i·cist, hy′dro·pon′ist** *n.*

hy·dro·qui·none (hī′drō-kwĭ-nōn′, -kwĭn′ōn′) also **hy·dro·quin·ol** (-kwĭn′ôl′, -ōl′) *n.* A white crystalline compound, $C_6H_4(OH)_2$, used as a photographic developer, antioxidant, stabilizer, and reagent.

hy·dro·scope (hī′drə-skōp′) *n.* An optical device used for viewing objects much below the surface of water. —**hy′dro·scop′ic** (-skŏp′ĭk) *adj.*

hy·dro·sol (hī′drə-sôl′, -sōl′) *n.* A sol with water as the dispersing medium. [HYDRO- + SOL(UTION).] —**hy′dro·sol′ic** (-sŏl′ĭk) *adj.*

hy·dro·sphere (hī′drə-sfîr′) *n.* The waters of the earth distinguished from the lithosphere and the atmosphere. —**hy′dro·spher′ic** (-sfîr′ĭk, -sfĕr′-) *adj.*

hy·dro·stat·ic (hī′drə-stăt′ĭk) also **hy·dro·stat·i·cal** (-ĭ-kəl) *adj.* Of or pertaining to hydrostatics. —**hy′dro·stat′i·cal·ly** *adv.*

hy·dro·stat·ics (hī′drə-stăt′ĭks) *n.* *(used with a sing. verb).* The statics of fluids, esp. incompressible fluids.

hy·dro·sul·fate (hī′drə-sŭl′fāt′) *n.* A salt formed by the union of sulfuric acid with an alkaloid or other organic base.

hy·dro·sul·fide (hī′drə-sŭl′fīd′) *n.* A chemical compound derived from hydrogen sulfide by replacement of one of the hydrogen atoms with a basic radical or base.

hy·dro·sul·fite (hī′drə-sŭl′fīt′) *n.* **1.** A salt of hyposulfurous acid. **2.** Sodium hydrosulfite.

hy·dro·sul·fu·rous acid (hī′drō-sŭl-fyo͝or′əs, -sŭl′fər-əs) *n.* Hyposulfurous acid.

hy·dro·tax·is (hī′drə-tăk′sĭs) *n.* *Biol.* Movement of an organism in response to moisture. —**hy′dro·tac′tic** (-tăk′tĭk) *adj.*

hy·dro·ther·a·peu·tics (hī′drə-thĕr′ə-pyo͞o′tĭks) *n.* *(used with a sing. verb).* Hydrotherapy. —**hy′dro·ther′a·peu′tic** *adj.*

hy·dro·ther·a·py (hī′drə-thĕr′ə-pē) *n.*, *pl.* **-pies.** The medical use of water in the treatment of certain diseases.

hy·dro·ther·mal (hī′drə-thûr′məl) *adj.* **1.** Of or relating to hot water. **2.** *Geol.* **a.** Of or relating to hot magmatic emanations that are rich in water. **b.** Of or relating to the rocks, ore deposits, and springs produced by such emanations. —**hy′dro·ther′mal·ly** *adv.*

hy·dro·tho·rax (hī′drə-thôr′ăks′, -thōr′-) *n.* The presence of serous fluid from the blood in one or both pleural cavities, often associated with cardiac failure.

hy·drot·ro·pism (hī-drŏt′rə-pĭz′əm) *n.* Growth or movement of an organism in response to water. —**hy′dro·tro′pic** (hī′drə-trō′pĭk, -trŏp′ĭk) *adj.* —**hy′dro·tro′pi·cal·ly** *adv.*

hy·drous (hī′drəs) *adj.* Containing water, esp. that of crystallization or hydration.

hy·drox·ide (hī-drŏk′sīd′) *n.* A chemical compound containing the hydroxyl group.

hydroxide ion *n.* The ion OH^-, characteristic of basic hydroxides.

hy·drox·y (hī-drŏk′sē) *adj.* Containing the hydroxyl group, as an acid. [< HYDROXYL.]

hy·drox·yl (hī-drŏk′sĭl) *n.* The univalent radical or group OH, characteristic of bases, certain acids, phenols, alcohols, carboxylic and sulfonic acids, and amphoteric compounds. [HYDR(O)- + OX(YGEN) + -YL.] —**hy′drox·yl′ic** (hī′drŏk-sĭl′ĭk) *adj.*

hy·drox·yl·a·mine (hī-drŏk′sə-lə-mēn′, hī′drŏk-sĭl′ə-mēn′) *n.* A colorless crystalline compound, NH_2OH, explosive when heated above 130°C, that is used as a reducing agent and in organic synthesis.

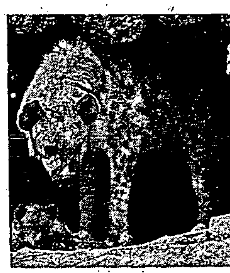
hy·drox·yl·ate (hī-drŏk′sə-lāt′) *tr.v.* **-at·ed, -at·ing, -ates.** To introduce the hydroxyl radical into. —**hy·drox′y·la′tion** *n.*

hydroxyl ion *n.* A hydroxide ion.

hy·dro·zo·an (hī′drə-zō′ən) *n.* Any of numerous coelenterates of the class Hydrozoa, which includes the hydroids, hydrocorals, and siphonophores. —*adj.* Of, pertaining to, or belonging to the class Hydrozoa. [< NLat. *Hydrozoa*, class name : HYDRO- + Gk. *zōia*, pl. of *zōion*, animal.]

Hy·drus (hī′drəs) *n.* A constellation in the Southern Hemisphere near Tucana and Mensa. [Lat. < Gk. *hudros*, water serpent.]

hy·e·na also **hy·ae·na** (hī-ē′nə) *n.* Any of several carnivorous mammals of the genera *Hyaena* or *Crocuta*, of Africa and Asia, having powerful jaws, relatively short hind limbs, and coarse hair. [ME *hiena* < Med. Lat. < Lat. *hyaena* < Gk. *huaina* < *hys*, hog.]



hyena

hy·e·tal (hī′ĭ-tl) *adj.* Of or relating to rain or to rainy regions. [< Gk. *huetos*, rain.]

Hy·ge·ia (hī-jē′ə) *n.* *Gk. Myth.* The goddess of health. [Gk. *Hugieia* < *hugiēs*, healthy.]

hy·giene (hī′jēn′) *n.* **1.** The science of health and the prevention of disease. **2.** Conditions and practices that serve to promote or preserve health. [Fr. *hygiène* and NLat. *hygiena*, both < Gk. *hugieinos*, healthful < *hugiēs*, healthy.] —**hy·gien′ist** (hī-jē′nĭst, hī′jē′-, hī-jĕn′ĭst) *n.*

hy·gi·en·ic (hī′jē-ĕn′ĭk, hī-jĕn′-) *adj.* **1.** Of or pertaining to hygiene. **2.** Tending to promote or preserve health. **3.** Sanitary. —**hy′gi·en′i·cal·ly** *adv.*

hy·gi·en·ics (hī′jē-ĕn′ĭks, hī-jĕn′-) *n.* *(used with a sing. verb).* Hygiene (sense 1).

hygro– *pref.* Moisture; humidity: *hygroscope.* [< Gk. *hugros*, moist.]

hy·gro·graph (hī′grə-grăf′) *n.* An automatic hygrometer that records variations in atmospheric humidity.

hy·grom·e·ter (hī-grŏm′ĭ-tər) *n.* Any of several instruments that measure atmospheric humidity. —**hy′gro·met′ric** (hī′grə-mĕt′rĭk) *adj.* —**hy·grom′e·try** *n.*

hy·gro·scope (hī′grə-skōp′) *n.* An instrument that measures changes in atmospheric moisture.

hy·gro·scop·ic (hī′grə-skŏp′ĭk) *adj.* Readily absorbing moisture, as from the atmosphere. —**hy′gro·scop′i·cal·ly** *adv.* —**hy′gro·sco·pic′i·ty** (-skō-pĭs′ĭ-tē) *n.*

hy·ing (hī′ĭng) *v.* A present participle of **hie.**

hy·lo·zo·ism (hī′lə-zō′ĭz′əm) *n.* The philosophical doctrine that life is a property or derivative of matter, that life and matter are inseparable, or that matter possesses a spiritual component. [Gk. *hulē*, matter + Gk. *zoē*, life + -ISM.] —**hy′lo·zo′ic** *adj.* —**hy′lo·zo′ist** *n.* —**hy′lo·zo·is′tic** (-zō-ĭs′tĭk) *adj.*

hy·men (hī′mən) *n.* A membranous fold of tissue partly or completely occluding the external vaginal orifice. [LLat. < Gk. *humēn*, membrane.] —**hy′men·al** *adj.*

Hy·men (hī′mən) *n.* *Gk. Myth.* The god of marriage. [Lat. < Gk. *Humēn.*]

hy·me·ne·al (hī′mə-nē′əl) *adj.* Of or pertaining to a wedding or marriage. —*n.* A wedding song or poem. [Lat. *hymenaeus* < Gk. *humēnaios* < *Humēn*, Hymen.] —**hy′me·ne′al·ly** *adv.*

hy·me·ni·um (hī-mē′nē-əm) *n.*, *pl.* **-ni·a** (-nē-ə) or **-ni·ums.** The spore-bearing layer of the fruiting body of certain fungi, containing asci or basidia. [NLat. < Gk. *humēn*, membrane.] —**hy·me′ni·al** (-əl) *adj.*

hy·me·nop·ter·an (hī′mə-nŏp′tər-ən) also **hy·me·nop·ter·on** (-tə-rŏn′) *n.* An insect of the order Hymenoptera, characteristically having two pairs of membranous wings and